

Remarks

Claims 17, 18, 20, 22-26 and 36-45 are pending. The Applicants respectfully request entry of this amendment, as it places the claims in format for allowance as overcoming the pending rejections. In addition, should the Examiner find that the claims are not allowable, the amendment and terminal disclaimer place the claims in better form for consideration on appeal, and therefore the amendment should be entered.

**Double Patenting**

The claims have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims of co-pending Application 10/963,994, in co-pending Application 10/338,083, and in co-pending Application 11/008,091 and are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of US Patent No. 7,101,974.

A terminal disclaimer is hereby enclosed, and the rejection should be withdrawn.

**Claim Rejections – 35 U.S.C. § 102**

Claims 17-20, 23, 33, 36, 38, 40, 41, 44 and 49 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent 6,171,787 (the '787 patent) to Wiley.

The Examiner's position appears to be that the claims read on heterotrimers of TNFSF proteins, where monomers from different types of TNFSF proteins can be included in the heterotrimer. As such, the Examiner reasons, wild type TNF- $\gamma$  of the '787 patent will exchange *in vivo* with other TNFSF members to form heterotrimers that do not activate receptor signaling.

As a preliminary matter, the Applicants respectfully disagree. TNF- $\gamma$  will not exchange with other members of the TNFSF (e.g. non-TNF- $\gamma$  members of the family) and form heterotrimers with a 90% decrease in receptor activation. Consider for a moment the hypothesis that wild-type TNF- $\gamma$  exchanges *in vivo* with other TNFSF members to form heterotrimers that do not activate receptor signaling. If such a hypothesis was true, then a very significant percentage of TNFSF proteins *in vivo* would exist as an inactive heterotrimer, and therapeutics such as Remicade® (an antibody which targets TNF- $\alpha$  for rheumatoid arthritis treatment) and the '974 Patent would be unnecessary because TNF- $\alpha$  would already be inactive. Applicants could find no teaching or suggest in the '787 patent or

publication to support the assumption put forth in the Office Action that TNF-gamma inherently exchanges with other TNFSF members, or that such TNFSF heterotrimers inherently have a 50% or 90% decrease in receptor activation.

However, in the interests of furthering prosecution, claims 17 and 18 have been amended to recite that the monomers of the TNFSF proteins are all of a specific TNFSF, and the rejection should be withdrawn.

The Office Action cited Col. 2, lines 12-14 teaches "an engineered soluble version of TNF-gamma, as well as cell surface expressed form of TNF-gamma." Applicants respectfully submit that this paragraph teaches the wild-type TNF-gamma that has been "engineered" to express in a host cell. The Office Action also cites the '787 as teaching recombinant polypeptides (col. 11, lines 1-11) and "synthetic peptides" (col. 11, lines 12-15). Applicants respectfully submit that these paragraphs only teach methods of making the wild-type sequence disclosed elsewhere in the '787 patent, and do not teach any variant TNFSF protein. A "synthetic peptide" is merely a peptide made by chemical means – just like "synthetic water" is taking two parts hydrogen gas and mixing it with one part oxygen gas, adding heat to form H<sub>2</sub>O. A "synthetic" molecule, a "recombinant" molecule, or a naturally produced and purified molecule will have inherent characteristics regardless of the method of production, as pointed out by the Office Action on page 6 (citing *In re Papesch* and *In re Von Schickh*).

The Office Action in the paragraph bridging pages 6-7 that the '787 patent discloses synthetic fragments with or without substitutions, which inhibit activation of the TNFSF polypeptide or the TNFSF receptor, citing col. 4, lines 31-39 and col. 31, lines 66 – col. 32, line 21). Applicants respectfully disagree with this characterization of the '787 patent. The '787 patent does not actually disclose any synthetic peptide sequence. Columns 31-32 merely speculate that one of skill in the art could make peptides that might be used "as agonists and antagonists." However, no where in the '787 patent is there a disclosure of how one would actually make an antagonist, let alone an antagonist which operates by exchanging *in vivo* to form a dominant negative heterotrimer. Likewise, column 4 broadly states that a "compound which inhibits activation of the TNF-gamma polypeptide is provided." However, Applicants are unable to find any example in the '787 patent where Wiley actually made a TNF-gamma inhibiting compound, or any further teaching on how one of skill in the art could make such a TNF-gamma inhibiting compound. The only sequences taught or suggested in the '787 patent

are wild-type sequences, and these do not exchange with other TNFSF sequences to form a heterotrimer with 50% or 90% decreased receptor activation.

The Office Action states, "since inhibitors that bind to soluble TNFSF polypeptides that normally bind to TNFSF receptors are contemplated, the limitations of claims 20 and 44 have been met." Applicants respectfully submit that inhibitors binding to a homotrimer of a TNFSF polypeptide is not the same as a TNFSF variant that exchanges *in vivo* with a wild-type TNFSF polypeptide to form a TNFSF heterotrimer. The sequences disclosed in the '787 patent do not inherently meet the limitations of the pending claims.

As the Examiner is aware, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.' *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art)." MPEP §2112(IV) (emphasis in original). Applicants respectfully submit that nothing in the '787 patent teaches or suggests the present claims, or inherently meet the claim limitations, and the rejection should be withdrawn.

MORGAN, LEWIS & BOCKIUS LLP

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Customer No.: 67374

Morgan, Lewis & Bockius LLP  
One Market, Spear Street Tower  
San Francisco, CA 94105  
Telephone: (415) 442-1000  
Facsimile: (415) 442-1001

By:

  
Robin M. Silva, Reg. No. 38,304

Attorney of Record for Applicant

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